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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/766,442	01/19/2001	Jean-Christophe Francis Audonnet	454313-3154.2	8693

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EXAMINER	
ANGELL, JON E	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/766,442	AUDONNET ET AL.	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,5 and 16-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,5 and 16-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 January 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. This Action is in response to the communication filed on 1/21/04. The amendment has been entered. Claims 1, 4, 5 and 16-38 are currently pending in the application and are examined herein.

2. The finality of the previous Office Action is withdrawn, in view of the new rejections set forth herein.

3. The declaration filed on 1/21/04 under 37 CFR 1.131 is sufficient to overcome the Taylor reference, as well as any other reference that does not teach that two recombinant bovine vaccines can be used in combination. However, as indicated herein US Patent 6,376,473 (Audonnet) teaches a bovine vaccine that can comprise two plasmids, each expressing an immunogen of a bovine pathogen. Therefore, the declaration does not overcome the Audonnet reference, set forth below.

4. As indicated above, the declaration submitted 1/21/04 is sufficient to overcome any reference that does not teach a bovine vaccine comprising a plasmid vaccine in combination with a lipid molecule and another recombinant vaccine. However, upon further review of the prior art, it was found that a bovine vaccine for BRSV wherein the vaccine comprises two plasmids which express immunogens of the bovine pathogen was known in the art (see Audonnet). Therefore, the declaration is not sufficient to overcome the Audonnet reference. As such the only issues remaining is would one of ordinary skill in the art be motivated to add a cationic lipid, such as DMRIE/DOPE (as well as other adjuvants and modifications to increase efficacy of the vaccine) to the vaccine taught by Audonnet; and would there be an expectation of success?

As indicated below, all of the adjuvants added to the vaccine, as well as all of the medications to the to the immunogen(s) were techniques well known in the prior art for increasing the efficacy of vaccines. Therefore, one of ordinary skill in the art would have been motivated to make the changes to the Audonnet vaccine in order to increase the efficacy of the vaccine. Furthermore, one of ordinary skill would have had a reasonable expectation of success.

Claim Objections

5. Claim 17 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Specifically, claim 17 does not further limit claim 16 because the limitation set forth in claim 17 are present in claim 1, from which claim 16 depends and as such must be a limitation of claim 16.

6. Claim 29 is objected to because it is believed the language of claim 29 could be clearer. Specifically, the claim recites the phrase "BRSV is optimized by substitution, by a heterologous sequence, of the signal sequence of the F antigen..." (See lines 2-3 of the claim). It is noted that changing the claim to read, "BRSV is optimized by substitution of a heterologous sequence for the signal sequence of the F antigen..." would obviate this objection. It is noted that although the current claim is not perfectly clear, it does not rise to the level of being indefinite and as such does not require rejection under 35 USC 112, second paragraph.

Double Patenting

7. Claims 1, 4, 5 and 16-38 are directed to an invention not patentably distinct from claims 1-13 of commonly assigned US Patent No. 6,376,473 B1 (as set forth below). Specifically, the instant claims are drawn to a method of inducing an immune response in a bovine using a composition comprising (i) a plasmid that expresses an immunogen of a bovine pathogen, (ii) a cationic lipid (such as DOPE), and (iii) a recombinant vaccine against a bovine pathogen. The claims of US Patent No. 6,376,473 B1 are drawn to an immunogenic composition and method for inducing an immune response in a bovine wherein a the immunogenic composition comprises a plasmid that expresses an immunogen of a bovine pathogen (specifically BRSV-F) and also encompass a composition comprising a second plasmid that expresses an immunogen of a bovine pathogen (specifically, BRSV-G). Although the '473 patent does not teach the addition of any other substances to the immunogenic composition, all of the additional substances encompassed by the instant claims (including a cationic lipid, such as DOPE) were known in the art as adjuvants that could increase the immunological response of a subject to an immunogen (as indicated below). Therefore, the instant claims are not patently distinct from the claims of the '473 patent.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned US Patent 6,376,473 B1, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this

issue, the assignee is required under 35 U.S.C. 103(c) and 37 CFR 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 1, 4, 5, and 16-38 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 84-118 of copending Application No. 09/760,574. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims the '574 application are drawn to a vaccine comprising a plasmid which encodes and expresses a immunogen for a bovine pathogen in combination with a cationic lipid (e.g., see claim 84). Furthermore, a dependent claim adds

the additional limitation that the vaccine comprises a second plasmid which expresses a pathogen of a bovine pathogen (e.g., see claim 99).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

10. Additionally, claims 1, 4, 5, 16-18, 21, 27, 28, 32, 33 and 36-38 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 of U.S. Patent No. 6,376,473 B1 (Audonnet et al.) in view of Klavinskis et al. (1999).

It is noted that the invention appears to be an improved vaccine for a bovine pathogen (BRSV) wherein the improvement is the addition of a lipid complex (such as DMRIE/DOPE) to the vaccine. As mentioned below, the lipid complex DMRIE/DOPE was known to act as an adjuvant as well as a facilitator of DNA delivery into cells. Therefore, for the reasons set forth below, the instant claims are obvious in view of the prior art.

The claims are drawn to a DNA vaccine against a bovine pathogen comprising (a)(i) a plasmid that contains and expresses a nucleotide sequence encoding an immunogen of a bovine pathogen; (a)(ii) a cationic lipid; and (b) an inactivated, attenuated live, subunit or recombinant vaccine or immunogenic composition against a bovine pathogen (e.g., see claim 1); wherein the vaccine further comprises DOPE (claims 18); wherein the bovine pathogen is BRSV (e.g., see claim 4); wherein the immunogen is BRSV-F or BRSV-G (e.g., claim 5).

Audonnet teaches a vaccine for BRSV comprising at least one plasmid that contains and expresses in vivo a nucleic acid molecule having sequences encoding BRSV-F, or BRSV-G or

BRSV-F and –G proteins (e.g., see abstract and claims 5-8). It is respectfully pointed out that Audonnet clearly encompasses a vaccine comprising two plasmids each of which encodes a bovine antigen (specifically BRSV-F and BRSV-G). Furthermore instant claim 1 is encompasses a vaccine comprising (i) a plasmid which encodes and expresses an immunogen of a bovine pathogen, (ii) a cationic lipid, and (iii) a recombinant vaccine against a bovine pathogen (which encompasses a plasmid that expresses an immunogen of BRSV).

Audonnet does not teach that the vaccine comprises a cationic lipid, or a cationic lipid complex.

Klavinskis teaches a plasmid DNA vaccine complexed with the lipid DMRIE/DOPE which results in the enhanced expression of the encoded protein when administered to the respiratory tract of an animal, and which results in the increased circulating levels of specific IgA and IgG (e.g., see abstract). Klavinskis specifically teaches, "Cytofectins [the DMRIE/DOPE complex] may also provide a secondary role as an adjuvant, facilitating uptake of plasmid DNA by APCs or creating inflammation." (See p. 259, second column). Therefore, Klavinskis teaches that the DMRIE/DOPE lipid complex can be useful for 1) increasing the uptake of plasmids—resulting in an increased expression of the encoded protein (in this case, increased expression of the immunogen); and 2) as an adjuvant for increasing the immune response to the immunogen(s).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to combine the teachings of Audonnet and Klavinskis to create the invention of the instant claims with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to combine the references in order to increase the uptake of the plasmid vaccine into the target cells—resulting in the

increased expression of the encoded pathogens (here, BRSV-F and/or BRSV-G) and to stimulate the host's immune system in order to get an increased immune response against the pathogens.

11. Claims 1 and 19 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 of U.S. Patent No. 6,376,473 B1 (Audonnet) in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Xiang et al. (Immunity 1995, 2:129-135; IDS reference BF) and Baker et al. (US Patent 5,106,733; previously cited).

It is noted that the instant claims appear to be drawn to an improved vaccine for a bovine pathogen (BRSV) wherein the improvement is the addition of a lipid complex (such as DMRIE/DOPE) to the vaccine (as mentioned above) with the addition of bovine GM-CSF or a plasmid encoding bovine GM-CSF to the vaccine. GM-CSF was known to act as an adjuvant for vaccine compositions. Therefore, for the reasons set forth below, the instant claims are obvious in view of the prior art.

Claims 1 and 5 are obvious in view of the teachings of Audonnet and Klavinskis as mentioned above.

As mentioned above, Audonnet teaches a BRSV plasmid vaccine and Klavinskis teaches that DMRIE/DOPE lipid complexes which can be used to increase plasmid uptake and also as an adjuvant in a vaccine composition.

Neither Audonnet nor Klavinskis teach that the vaccine composition can comprise bovine GM-CSF or a plasmid encoding bovine GM-CSF.

Xiang teaches a method for enhancing the immune response to a DNA vaccine by co-administering a plasmid vaccine (here, a plasmid expressing the glycoprotein of rabies virus in vivo) and a plasmid expressing GM-CSF (here, mouse GM-CSF) (see p. 129, abstract; p. 130, Table 1; and p.132, under "A plasmid vector expressing mouse GM-CSF enhances the efficacy of the DNA vaccine to Rabies Virus). Xiang teaches that the mouse GM-CSF enhances the efficacy of the vaccine (see p. 132).

Xiang does not teach that the GM-GMCSF is bovine GM-CSF.

Baker teaches the cDNA sequence of bovine GM-CSF and methods of expressing bovine GM-CSF in a cell using an expression vector as well as methods for purifying the recombinant bovine GM-CSF (see Figure 1; column 1, lines 55-68; and column 6, line 13 through column 8, line 70). Baker teaches that bovine GM-CSF can be useful as "a therapeutic agent treating various cytopenias, and its apparent effect upon mature granulocytes and macrophages... [and] therapeutic compositions comprising recombinant bGM-CSF or active homologues could be employed to augment immune responsiveness to infectious pathogens or to assist in reconstituting normal blood cell populations following viral infection or other conditions resulting in hematopoietic cell suppression." (See column 1, lines 41-53).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to combine the teachings of the cited references to create the invention of the instant claims with a reasonable expectation of success. It is noted that the recombinant bGM-CSF could be purified and used in the vaccine in its proteinaceous form, or the cDNA encoding bGM-CSF (taught by Baker) could be cloned into the bovine expression plasmid taught by

Audonnet, which could then be with the vaccine complex to transfect and express bGM-CSF in bovine cells with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to add to a bovine vaccine composition bGM-CSF or a plasmid which encodes and expresses bGM-CSF in bovine cells because 1) GM-CSF was known to act as an adjuvant in vaccine compositions and 2) the prior art indicates that bGM-CSF could be used to augment immune responsiveness to infectious pathogens (i.e. could be an adjuvant).

12. Claims 1, 5, 22, 25, 26 and 31 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 of U.S. Patent No. 6,376,473 B1 (Audonnet) in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Li (WO 96/40945; IDS reference AL).

It is noted that the instant claims appear to be drawn to an improved vaccine for a bovine pathogen (BRSV) wherein the improvement comprises 1) the addition of a lipid complex (such as DMRIE/DOPE) to the vaccine (as mentioned above); 2) wherein a transmembrane of one of the pathogens has been deleted; and 3) wherein the plasmid vaccine further comprises the intron II of the rabbit beta-globin gene as a stabilizing intron. However, it was known in the prior art that deleting the transmembrane portion of the BRSV-F gene and including the intron II of the rabbit beta-globin gene could improve the vaccine. Therefore, for the reasons set forth below, the instant claims are obvious in view of the prior art.

Claims 1and 5 are obvious in view of the teachings of Audonnet and Klavinskis as mentioned above.

As mentioned above, Audonnet teaches a BRSV plasmid vaccine and Klavinskis teaches that DMRIE/DOPE lipid complexes which can be used to increase plasmid uptake and also as an adjuvant in a vaccine composition.

Neither Audonnet nor Klavinskis teach that the vaccine composition comprises a BRSV pathogen wherein the pathogen has a transmembrane domain deleted.

Li teaches a nucleic acid RSV vaccine comprising a plasmid containing a nucleotide sequence which encodes an RSV F protein from which the transmembrane region is absent (see p. 5, lines 25-35). Li teaches that the deletion of the trans membrane region results in a secreted form of the RSV F protein (see p. 5, line 35 through p. 6, line 1). Li teaches deletion of the transmembrane domain increases the efficacy of the vaccine (see p. 27, lines 2-21). In fact, only the vaccine comprising the deletion of the transmembrane of the F protein result in complete protection (see p. 27, lines 14-21). Additionally the vaccine comprises the nucleotide sequence of the rabbit beta-globin intron II, to prevent aberrant mRNA splicing (see p. 6, lines 2-9). The rabbit beta-globin intron II sequence prevents aberrant mRNA splicing, thus stabilizing the mRNA and enhancing the immunoprotective ability of the vaccine (see p. 6, lines 26-32).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to combine the teachings of the cited references to create the invention of the instant claims with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to delete the transmembrane region of the BRSV-F gene and to include intron II or the rabbit beta-globin gene in the plasmid in order to enhance the immunoprotective ability of the vaccine, as taught by Li.

13. Claims 1, 5, 23, 24, 29 and 30 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 of U.S. Patent No. 6,376,473 B1 (Audonnet) in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Choi et al. (Virology 1998, 250:230-240; IDS reference BS).

It is noted that the instant claims appear to be drawn to an improved vaccine for a bovine pathogen (BRSV) wherein the improvement comprises 1) the addition of a lipid complex (such as DMRIE/DOPE) to the vaccine (as mentioned above); 2) a substitution of the signal sequence with a heterologous tPA signal sequence. However, it was known in the prior art that the human tPA signal sequence could improve a vaccine. Therefore, for the reasons set forth below, the instant claims are obvious in view of the prior art.

Claims 1 and 5 are obvious in view of the teachings of Audonnet and Klavinskis as mentioned above.

As mentioned above, Audonnet teaches a BRSV plasmid vaccine and Klavinskis teaches that DMRIE/DOPE lipid complexes which can be used to increase plasmid uptake and also as an adjuvant in a vaccine composition. Audonnet specifically teaches that the vaccine can comprise plasmid(s) which encode and express BRSV-F and/or BRSV-G.

Neither Audonnet nor Klavinskis teach that the plasmid vaccine comprises and expresses a heterologous tPA signal sequence in place of the normal signal sequence of BRSV-F or BRSV-G.

Choi teaches Choi teaches the human tPA signal sequence can enhance the expression of an immunogen and enhance the host's immune response to the immunogen when the immunogen is expressed as a tPA/immunogen fusion protein (see p. 233, Table 2 wherein the tPA/immunogen fusion (WRG/4) results in increased IgG response compared the wild-type immunogen (pcDNA/4)).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to combine the teachings of the cited references to create the invention of the instant claims with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to include a heterologous tPA signal sequence as a fusion with the pathogenic gene (substituting the normal BRSV-F or NRSV-G signal sequence with the human tPA signal sequence) in the plasmid in order to enhance the expression of the immunogen and enhance the host's immune response to the immunogen.

14. Claims 1, 5 and 34 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 of U.S. Patent No. 6,376,473 B1 (Audonnet) in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Xiang et al. (Immunity 1995, 2:129-135; IDS BF), Baker et al. (US Patent 5,106,733; 1992), Li (WO 96/40945; IDS AL), and Choi et al. (Virology 1998, 250:230-240; IDS BS).

It is noted that the invention appears to be an improved vaccine for a bovine pathogen (BRSV) wherein the improvement comprises: the addition of a lipid complex (such as DMRIE/DOPE) to the vaccine; the a gene encoding the BRSV-F gene with a substitution of a human tPA signal sequence in place of the normal signal sequence; a second plasmid encoding the BRSV-G gene with a substitution of a human tPA signal sequence in place of the normal signal sequence; bovine GM-CSF or a plasmid which expresses bGM-CSF in bovine cells; wherein the transmembrane signal sequence of the pathogenic gene is deleted; and a stabilizing intron, such as intron II of the rabbit beta-globin gene. As mentioned and summarized below, all of the modifications were known in the prior art. Therefore, for the reasons set forth below, the instant claims are obvious in view of the prior art.

Audonnet teaches a vaccine for BRSV comprising at least one plasmid that contains and expresses in vivo (in a bovine host cell) a nucleic acid molecule having sequences encoding BRSV-F, or BRSV-G or BRSV-F and –G proteins (e.g., see abstract and claims 5-8).

Audonnet does not teach that the BRSV vaccine comprises a cationic lipid, or a cationic lipid complex.

Klavinskis teaches a plasmid DNA vaccine complexed with the lipid DMRIE/DOPE which results in the enhanced expression of the encoded protein when administered to the respiratory tract of an animal, and which results in the increased circulating levels of specific IgA and IgG (e.g., see abstract). Klavinskis specifically teaches, "Cytofectins [the DMRIE/DOPE complex] may also provide a secondary role as an adjuvant, facilitating uptake of plasmid DNA by APCs or creating inflammation." (See p. 259, second column). Therefore, Klavinskis teaches that the DMRIE/DOPE lipid complex can be useful for 1) increasing the uptake of plasmids—

resulting in an increased expression of the encoded protein; and 2) as an adjuvant for increasing the immune response to pathogens.

Neither Audonnet nor Klavinskis teaches that the vaccine composition can comprise bovine GM-CSF or a plasmid encoding bovine GM-CSF.

Xiang teaches a method for enhancing the immune response to a DNA vaccine by co-administering a plasmid vaccine (here, a plasmid expressing the glycoprotein of rabies virus in vivo) and a plasmid expressing GM-CSF (here, mouse GM-CSF) (see p. 129, abstract; p. 130, Table 1; and p.132, under "A plasmid vector expressing mouse GM-CSF enhances the efficacy of the DNA vaccine to Rabies Virus). Xiang teaches that the mouse GM-CSF enhances the efficacy of the vaccine (see p. 132).

Xiang does not teach that the GM-GMCSF is bovine GM-CSF.

Baker teaches the cDNA sequence of bovine GM-CSF and methods of expressing bovine GM-CSF in a cell using an expression vector as well as methods for purifying the recombinant bovine GM-CSF (see Figure 1; column 1, lines 55-68; and column 6, line 13 through column 8, line 70). Baker teaches that bovine GM-CSF can be useful as "a therapeutic agent treating various cytopenias, and its apparent effect upon mature granulocytes and macrophages... [and] therapeutic compositions comprising recombinant bGM-CSF or active homologues could be employed to augment immune responsiveness to infectious pathogens or to assist in reconstituting normal blood cell populations following viral infection or other conditions resulting in hematopoietic cell suppression." (See column 1, lines 41-53).

Audonnet, Klavinskis, Xiang and Baker do not teach that the vaccine composition comprises a BRSV pathogen wherein the pathogen has a transmembrane domain deleted or that the plasmid contains a stabilizing intron such as intron II of the rabbit beta-globin gene.

Li teaches a nucleic acid RSV vaccine comprising a plasmid containing a nucleotide sequence which encodes an RSV F protein from which the transmembrane region is absent (see p. 5, lines 25-35). Li teaches that the deletion of the trans membrane region results in a secreted form of the RSV F protein (see p. 5, line 35 through p. 6, line 1). Li teaches deletion of the transmembrane domain increases the efficacy of the vaccine (see p. 27, lines 2-21). In fact, only the vaccine comprising the deletion of the transmembrane of the F protein result in complete protection (see p. 27, lines 14-21). Additionally the vaccine comprises the nucleotide sequence of the rabbit beta-globin intron II, to prevent aberrant mRNA splicing (see p. 6, lines 2-9). The rabbit beta-globin intron II sequence prevents aberrant mRNA splicing, thus stabilizing the mRNA and enhancing the immunoprotective ability of the vaccine (see p. 6, lines 26-32).

Audonnet, Klavinskis, Xiang, Baker and Li do not teach that the vaccine composition comprises that the plasmid vaccine comprises and expresses a heterologous tPA signal sequence in place of the normal signal sequence of BRSV-F or BRSV-G.

Choi teaches Choi teaches the human tPA signal sequence can enhance the expression of an immunogen and enhance the host's immune response to the immunogen when the immunogen is expressed as a tPA/immunogen fusion protein (see p. 233, Table 2 wherein the tPA/immunogen fusion (WRG/4) results in increased IgG response compared the wild-type immunogen (pcDNA/4)).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to combine the teachings of the cited references to create the invention of the instant claims with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to make the modifications in order to create a better vaccine which confers a greater immune response to pathogen(s) (here, BRSV-F and/or BRSV-G) resulting in a greater degree of protective immunity to the pathogen.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. With respect to the rejection of claims under 35 USC 103 wherein US Patent No. 6,376,473 B1 (Audonnet et al.) is used as a reference (see below), it is noted that the applied reference (Audonnet) has a common assignee and a common inventor (Audonnet) with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

18. Claim1, 4, 5, 16-18, 21, 27, 28, 32, 33 and 36-38 are rejected under 35 U.S.C. 103(a) as being obvious over U.S. Patent No. 6,376,473 B1 (Audonnet et al.) in view of Klavinskis et al. (1999).

It is noted that the invention appears to be an improved vaccine for a bovine pathogen (BRSV) wherein the improvement is the addition of a lipid complex (such as DMRIE/DOPE) to

the vaccine. As mentioned below, the lipid complex DMRIE/DOPE was known to act as an adjuvant as well as a facilitator of DNA delivery into cells. Therefore, for the reasons set forth below, the instant claims are obvious in view of the prior art.

The claims are drawn to a DNA vaccine against a bovine pathogen comprising (a)(i) a plasmid that contains and expresses a nucleotide sequence encoding an immunogen of a bovine pathogen; (a)(ii) a cationic lipid; and (b) an inactivated, attenuated live, subunit or recombinant vaccine or immunogenic composition against a bovine pathogen (e.g., see claim 1); wherein the vaccine further comprises DOPE (claims 18); wherein the bovine pathogen is BRSV (e.g., see claim 4); wherein the immunogen is BRSV-F or BRSV-G (e.g., claim 5).

Audonnet teaches a vaccine for BRSV comprising at least one plasmid that contains and expresses in vivo a nucleic acid molecule having sequences encoding BRSV-F, or BRSV-G or BRSV-F and –G proteins (e.g., see abstract and claims 5-8). It is respectfully pointed out that Audonnet clearly encompasses a vaccine comprising two plasmids each of which encodes a bovine antigen (specifically BRSV-F and BRSV-G). Furthermore instant claim 1 is encompasses a vaccine comprising (i) a plasmid which encodes and expresses an immunogen of a bovine pathogen, (ii) a cationic lipid, and (iii) a recombinant vaccine against a bovine pathogen (which encompasses a plasmid that expresses an immunogen of BRSV).

Audonnet does not teach that the vaccine comprises a cationic lipid, or a cationic lipid complex.

Klavinskis teaches a plasmid DNA vaccine complexed with the lipid DMRIE/DOPE which results in the enhanced expression of the encoded protein when administered to the respiratory tract of an animal, and which results in the increased circulating levels of specific IgA

and IgG (e.g., see abstract). Klavinskis specifically teaches, "Cytofectins [the DMRIE/DOPE complex] may also provide a secondary role as an adjuvant, facilitating uptake of plasmid DNA by APCs or creating inflammation." (See p. 259, second column). Therefore, Klavinskis teaches that the DMRIE/DOPE lipid complex can be useful for 1) increasing the uptake of plasmids—resulting in an increased expression of the encoded protein (in this case, increased expression of the immunogen); and 2) as an adjuvant for increasing the immune response to the immunogen(s).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to combine the teachings of Audonnet and Klavinskis to create the invention of the instant claims with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to combine the references in order to increase the uptake of the plasmid vaccine into the target cells—resulting in the increased expression of the encoded pathogens (here, BRSV-F and/or BRSV-G) and to stimulate the host's immune system in order to get an increased immune response against the pathogens.

19. Claims 1 and 19 are rejected under 35 U.S.C. 103(a) as being obvious over U.S. Patent No. 6,376,473 B1 (Audonnet) in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Xiang et al. (Immunity 1995, 2:129-135) and Baker et al. (US Patent 5,106,733).

It is noted that the instant claims appear to be drawn to an improved vaccine for a bovine pathogen (BRSV) wherein the improvement is the addition of a lipid complex (such as DMRIE/DOPE) to the vaccine (as mentioned above) with the addition of bovine GM-CSF or a plasmid encoding bovine GM-CSF to the vaccine. GM-CSF was known to act as an adjuvant for

vaccine compositions. Therefore, for the reasons set forth below, the instant claims are obvious in view of the prior art.

Claims 1 and 5 are obvious in view of the teachings of Audonnet and Klavinskis as mentioned above.

As mentioned above, Audonnet teaches a BRSV plasmid vaccine and Klavinskis teaches that DMRIE/DOPE lipid complexes which can be used to increase plasmid uptake and also as an adjuvant in a vaccine composition.

Neither Audonnet nor Klavinskis teach that the vaccine composition can comprise bovine GM-CSF or a plasmid encoding bovine GM-CSF.

Xiang teaches a method for enhancing the immune response to a DNA vaccine by co-administering a plasmid vaccine (here, a plasmid expressing the glycoprotein of rabies virus in vivo) and a plasmid expressing GM-CSF (here, mouse GM-CSF) (see p. 129, abstract; p. 130, Table 1; and p.132, under "A plasmid vector expressing mouse GM-CSF enhances the efficacy of the DNA vaccine to Rabies Virus). Xiang teaches that the mouse GM-CSF enhances the efficacy of the vaccine (see p. 132).

Xiang does not teach that the GM-GMCSF is bovine GM-CSF.

Baker teaches the cDNA sequence of bovine GM-CSF and methods of expressing bovine GM-CSF in a cell using an expression vector as well as methods for purifying the recombinant bovine GM-CSF (see Figure 1; column 1, lines 55-68; and column 6, line 13 through column 8, line 70). Baker teaches that bovine GM-CSF can be useful as "a therapeutic agent treating various cytopenias, and its apparent effect upon mature granulocytes and macrophages... [and] therapeutic compositions comprising recombinant bGM-CSF or active homologues could be

employed to augment immune responsiveness to infectious pathogens or to assist in reconstituting normal blood cell populations following viral infection or other conditions resulting in hematopoietic cell suppression." (See column 1, lines 41-53).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to combine the teachings of the cited references to create the invention of the instant claims with a reasonable expectation of success. It is noted that the recombinant bGM-CSF could be purified and used in the vaccine in its proteinaceous form, or the cDNA encoding bGM-CSF (taught by Baker) could be cloned into the bovine expression plasmid taught by Audonnet, which could then be with the vaccine complex to transfect and express bGM-CSF in bovine cells with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to add to a bovine vaccine composition bGM-CSF or a plasmid which encodes and expresses bGM-CSF in bovine cells because 1) GM-CSF was known to act as an adjuvant in vaccine compositions and 2) the prior art indicates that bGM-CSF could be used to augment immune responsiveness to infectious pathogens (i.e. could be an adjuvant).

20. Claims 1, 5, 22, 25, 26 and 31 are rejected under 35 U.S.C. 103(a) as being obvious over U.S. Patent No. 6,376,473 B1 (Audonnet) in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Li (WO 96/40945).

It is noted that the instant claims appear to be drawn to an improved vaccine for a bovine pathogen (BRSV) wherein the improvement comprises 1) the addition of a lipid complex (such as DMRIE/DOPE) to the vaccine (as mentioned above); 2) wherein a transmembrane of one of

the pathogens has been deleted; and 3) wherein the plasmid vaccine further comprises the intron II of the rabbit beta-globin gene as a stabilizing intron. However, it was known in the prior art that deleting the transmembrane portion of the BRSV-F gene and including the intron II of the rabbit beta-globin gene could improve the vaccine. Therefore, for the reasons set forth below, the instant claims are obvious in view of the prior art.

Claims 1 and 5 are obvious in view of the teachings of Audonnet and Klavinskis as mentioned above.

As mentioned above, Audonnet teaches a BRSV plasmid vaccine and Klavinskis teaches that DMRIE/DOPE lipid complexes which can be used to increase plasmid uptake and also as an adjuvant in a vaccine composition.

Neither Audonnet nor Klavinskis teach that the vaccine composition comprises a BRSV pathogen wherein the pathogen has a transmembrane domain deleted.

Li teaches a nucleic acid RSV vaccine comprising a plasmid containing a nucleotide sequence which encodes an RSV F protein from which the transmembrane region is absent (see p. 5, lines 25-35). Li teaches that the deletion of the trans membrane region results in a secreted form of the RSV F protein (see p. 5, line 35 through p. 6, line 1). Li teaches deletion of the transmembrane domain increases the efficacy of the vaccine (see p. 27, lines 2-21). In fact, only the vaccine comprising the deletion of the transmembrane of the F protein result in complete protection (see p. 27, lines 14-21). Additionally the vaccine comprises the nucleotide sequence of the rabbit beta-globin intron II, to prevent aberrant mRNA splicing (see p. 6, lines 2-9). The rabbit beta-globin intron II sequence prevents aberrant mRNA splicing, thus stabilizing the mRNA and enhancing the immunoprotective ability of the vaccine (see p. 6, lines 26-32).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to combine the teachings of the cited references to create the invention of the instant claims with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to delete the transmembrane region of the BRSV-F gene and to include intron II or the rabbit beta-globin gene in the plasmid in order to enhance the immunoprotective ability of the vaccine, as taught by Li.

21. Claims 1, 5, 23, 24, 29 and 30 are rejected under 35 U.S.C. 103(a) as being obvious over U.S. Patent No. 6,376,473 B1 (Audonnet) in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Choi et al. (Virology 1998, 250:230-240).

It is noted that the instant claims appear to be drawn to an improved vaccine for a bovine pathogen (BRSV) wherein the improvement comprises 1) the addition of a lipid complex (such as DMRIE/DOPE) to the vaccine (as mentioned above); 2) a substitution of the signal sequence with a heterologous tPA signal sequence. However, it was known in the prior art that the human tPA signal sequence could improve a vaccine. Therefore, for the reasons set forth below, the instant claims are obvious in view of the prior art.

Claims 1 and 5 are obvious in view of the teachings of Audonnet and Klavinskis as mentioned above.

As mentioned above, Audonnet teaches a BRSV plasmid vaccine and Klavinskis teaches that DMRIE/DOPE lipid complexes which can be used to increase plasmid uptake and also as an

adjuvant in a vaccine composition. Audonnet specifically teaches that the vaccine can comprise plasmid(s) which encode and express BRSV-F and/or BRSV-G.

Neither Audonnet nor Klavinskis teach that the plasmid vaccine comprises and expresses a heterologous tPA signal sequence in place of the normal signal sequence of BRSV-F or BRSV-G.

Choi teaches Choi teaches the human tPA signal sequence can enhance the expression of an immunogen and enhance the host's immune response to the immunogen when the immunogen is expressed as a tPA/immunogen fusion protein (see p. 233, Table 2 wherein the tPA/immunogen fusion (WRG/4) results in increased IgG response compared the wild-type immunogen (pcDNA/4)).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to combine the teachings of the cited references to create the invention of the instant claims with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to include a heterologous tPA signal sequence as a fusion with the pathogenic gene (substituting the normal BRSV-F or NRSV-G signal sequence with the human tPA signal sequence) in the plasmid in order to enhance the expression of the immunogen and enhance the host's immune response to the immunogen.

22. Claims 1, 5 and 34 are rejected under 35 U.S.C. 103(a) as being obvious over U.S. Patent No. 6,376,473 B1 (Audonnet) in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Xiang et al. (Immunity 1995, 2:129-135),

Baker et al. (US Patent 5,106,733; 1992), Li (WO 96/40945), and Choi et al. (Virology 1998, 250:230-240).

It is noted that the invention appears to be an improved vaccine for a bovine pathogen (BRSV) wherein the improvement comprises: the addition of a lipid complex (such as DMRIE/DOPE) to the vaccine; the a gene encoding the BRSV-F gene with a substitution of a human tPA signal sequence in place of the normal signal sequence; a second plasmid encoding the BRSV-G gene with a substitution of a human tPA signal sequence in place of the normal signal sequence; bovine GM-CSF or a plasmid which expresses bGM-CSF in bovine cells; wherein the transmembrane signal sequence of the pathogenic gene is deleted; and a stabilizing intron, such as intron II of the rabbit beta-globin gene. As mentioned and summarized below, all of the modifications were known in the prior art. Therefore, for the reasons set forth below, the instant claims are obvious in view of the prior art.

Audonnet teaches a vaccine for BRSV comprising at least one plasmid that contains and expresses in vivo (in a bovine host cell) a nucleic acid molecule having sequences encoding BRSV-F, or BRSV-G or BRSV-F and –G proteins (e.g., see abstract and claims 5-8).

Audonnet does not teach that the BRSV vaccine comprises a cationic lipid, or a cationic lipid complex.

Klavinskis teaches a plasmid DNA vaccine complexed with the lipid DMRIE/DOPE which results in the enhanced expression of the encoded protein when administered to the respiratory tract of an animal, and which results in the increased circulating levels of specific IgA and IgG (e.g., see abstract). Klavinskis specifically teaches, "Cytofectins [the DMRIE/DOPE complex] may also provide a secondary role as an adjuvant, facilitating uptake of plasmid DNA

by APCs or creating inflammation." (See p. 259, second column). Therefore, Klavinskis teaches that the DMRIE/DOPE lipid complex can be useful for 1) increasing the uptake of plasmids—resulting in an increased expression of the encoded protein; and 2) as an adjuvant for increasing the immune response to pathogens.

Neither Audonnet nor Klavinskis teaches that the vaccine composition can comprise bovine GM-CSF or a plasmid encoding bovine GM-CSF.

Xiang teaches a method for enhancing the immune response to a DNA vaccine by co-administering a plasmid vaccine (here, a plasmid expressing the glycoprotein of rabies virus in vivo) and a plasmid expressing GM-CSF (here, mouse GM-CSF) (see p. 129, abstract; p. 130, Table 1; and p.132, under "A plasmid vector expressing mouse GM-CSF enhances the efficacy of the DNA vaccine to Rabies Virus). Xiang teaches that the mouse GM-CSF enhances the efficacy of the vaccine (see p. 132).

Xiang does not teach that the GM-GMCSF is bovine GM-CSF.

Baker teaches the cDNA sequence of bovine GM-CSF and methods of expressing bovine GM-CSF in a cell using an expression vector as well as methods for purifying the recombinant bovine GM-CSF (see Figure 1; column 1, lines 55-68; and column 6, line 13 through column 8, line 70). Baker teaches that bovine GM-CSF can be useful as "a therapeutic agent treating various cytopenias, and its apparent effect upon mature granulocytes and macrophages... [and] therapeutic compositions comprising recombinant bGM-CSF or active homologues could be employed to augment immune responsiveness to infectious pathogens or to assist in reconstituting normal blood cell populations following viral infection or other conditions resulting in hematopoietic cell suppression." (See column 1, lines 41-53).

Audonnet, Klavinskis, Xiang and Baker do not teach that the vaccine composition comprises a BRSV pathogen wherein the pathogen has a transmembrane domain deleted or that the plasmid contains a stabilizing intron such as intron II of the rabbit beta-globin gene.

Li teaches a nucleic acid RSV vaccine comprising a plasmid containing a nucleotide sequence which encodes an RSV F protein from which the transmembrane region is absent (see p. 5, lines 25-35). Li teaches that the deletion of the trans membrane region results in a secreted form of the RSV F protein (see p. 5, line 35 through p. 6, line 1). Li teaches deletion of the transmembrane domain increases the efficacy of the vaccine (see p. 27, lines 2-21). In fact, only the vaccine comprising the deletion of the transmembrane of the F protein result in complete protection (see p. 27, lines 14-21). Additionally the vaccine comprises the nucleotide sequence of the rabbit beta-globin intron II, to prevent aberrant mRNA splicing (see p. 6, lines 2-9). The rabbit beta-globin intron II sequence prevents aberrant mRNA splicing, thus stabilizing the mRNA and enhancing the immunoprotective ability of the vaccine (see p. 6, lines 26-32).

Audonnet, Klavinskis, Xiang, Baker and Li do not teach that the vaccine composition comprises that the plasmid vaccine comprises and expresses a heterologous tPA signal sequence in place of the normal signal sequence of BRSV-F or BRSV-G.

Choi teaches Choi teaches the human tPA signal sequence can enhance the expression of an immunogen and enhance the host's immune response to the immunogen when the immunogen is expressed as a tPA/immunogen fusion protein (see p. 233, Table 2 wherein the tPA/immunogen fusion (WRG/4) results in increased IgG response compared the wild-type immunogen (pcDNA/4)).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to combine the teachings of the cited references to create the invention of the instant claims with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to make the modifications in order to create a better vaccine which confers a greater immune response to pathogen(s) (here, BRSV-F and/or BRSV-G) resulting in a greater degree of protective immunity to the pathogen.

Response to Arguments

23. Applicant's arguments, see pages 5-8 of the communication filed 1/21/04, with respect to the rejection(s)of claim(s) under 35 USC 103 have been fully considered and are persuasive. Specifically, Applicant arguments that the base reference (Taylor) did not teach a plasmid vaccine encoding an immunogen of a bovine pathogen are correct. Therefore, the rejections based on the teachings of Taylor have been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of the teachings of Audonnet et al., as indicated above.

24. Applicant's arguments filed 1/21/04 with respect to the provisional double patenting rejection of claims over claims in application 09/760,574 have been fully considered but they are not persuasive for the reasons indicated above. Furthermore, an additional Obvious-type double patenting rejection has been issued in view US Patent 6,376,473, for the reasons indicated above.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (571) 272-0756. The examiner can normally be reached on M-F (8:00-5:30) with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Art Unit 1635

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